Remarks

Claims 1-14 are pending in the subject application. By this Amendment, the applicants have amended claims 1, 2, 5, 8, 9 and 10. In addition, a new paper copy and computer readable form of the sequence listing is provided. No new matter has been added by these amendments. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-14 are currently before the Examiner for consideration.

The amendments set forth herein have been made to lend greater specificity to the claimed subject matter and to expedite prosecution. These amendments should not be taken to indicate the applicants' agreement with, or acquiescence in, the rejections of record. Favorable reconsideration of the claims now presented is earnestly solicited.

As an initial matter, the Office Action indicates that no drawings were submitted with the subject application. The 17 figures to which the specification refers were submitted at the time the application was filed under 35 U.S.C. §371. However, to expedite prosecution, new figures 1-17 are attached for consideration. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

The specification was objected to for failing to provide page numbers. The applicants respectfully submit that the copy of the application as filed included page numbers. To expedite prosecution, another copy of the specification as filed is being submitted with this Amendment. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

The Office Action indicates that the specification is not in compliance with 37 C.F.R. §1.821 through 1.825 with regard to nucleotide sequence and/or amino acid sequence disclosures. The amino acid sequences listed on page 9, lines 27-28 have been included in a new sequence listing. Accordingly, the applicants respectfully request reconsideration and withdrawal of this objection.

Claims 6, 7, 9, 13 and 14 have been rejected under 35 U.S.C. § 112, first paragraph. The Office Action indicates that the yeast transformation strains pIC9DP-hMK/SMD1168 and pPIC9-hPTN/GS115 are not readily reproducible. The applicants respectfully traverse this grounds for rejection because a person skilled in the art could readily make and use these strains by following the procedures as set forth in the applicants' specification. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-14 have been rejected under 35 U.S.C. §112, second paragraph as indefinite. The applicants respectfully submit that the use of the term "derived" does not render the claims indefinite. However, as noted above, the claims have been amended to delete reference to the term "derived." Accordingly, the applicants respectfully submit that this aspect of the rejection has been rendered moot.

With regard to the applicants' reference to "5' AOX1 and 3' AXO1," claims 2 and 10 have been amended to clarify that, consistent with the teachings in the specification, the sequences are 5' and 3' sequences within the AOX1 gene.

In view of the foregoing remarks and the amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph.

Claims 1-5, 8, and 10-12 have been rejected under 35 U.S.C. §103(a) as obvious over Davis *et al.* (WO 92/13951) in view of Tomomura *et al.* and Li *et al.* The applicants respectfully traverse this grounds of rejection because the cited references do not teach or suggest the current applicants' unique and advantageous vectors, transformants, and expression methods.

As noted by Examiner, the primary Davis *et al.* reference does not teach the use of an expression system to produce an intact MK family protein. The Examiner cites to Tomomura *et al.* and Li *et al.* to cure the deficiencies of Davis *et al.* Tomomura *et al.* simply teach the nucleotide sequences encoding MK1, MK2 and MK3. Li *et al.* teach the cloning and expression of MK family protein, PTN, as well as the nucleotide and amino acid sequences corresponding to the PTN protein.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to utilize the Davis methylotrophic yeast expression system to produce an MK family protein because such "would overcome the major problems associated with [an] *S. cerevisiae* expression system, such as loss of selection for plasmid maintenance and distribution." Moreover, exchanging the nucleotide sequence for human serum albumin with the nucleotide sequence for MK or PTN is a matter of "routine experimentation."

The applicants respectfully disagree and would like to respectfully point out to the Examiner how the instant invention is unique and non-obvious over the prior art and that the instant invention has several unexpected results that could not have been foreseen from the cited art.

As the instant specification describes at Page 2, lines 23 to 27, using the secretion signal unique to MK results in low yield and the predominance of sugar-bound MK (*i.e.*, the expression of intact MK protein is low). Accordingly, a unique and advantageous feature of the present invention involves the ligation of the MK protein cDNA downstream of the α1 factor gene of *S. cerevisiae* under the regulation of the AOX1 promoter from *P. pastoris*. (See the specification at page 3, lines 12-16). Surprisingly, the use of this particular signal sequence in combination with a gene encoding a mature MK family protein results in a marked increase in the expression of intact MK protein. Specifically, as discussed in Example 3, the expression level of MK produced using the α1 factor as the secretion signal (pPIC9K) was 100 times that detected using the PHO1 secretion signal (PHILS1-3AhMK) and 3 to 5 times that detected using the secretion signal unique to MK (PHILD4-hMK). Thus, the applicants' data demonstrate the unexpected advantages of the secretion signal.

Conversely, Davis *et al.* suggest that the secretion signal may be selected either from the *S. cerevisiae* AMF or the native protein secretion signal. See Abstract, lines 3-4 as well as p. 7, lines 9-20; p. 11, lines 29-34; and p. 13, lines 3-29. Thus, the Davis *et al.* reference teaches away from the critically of the secretion signal sequence, in contrast to Applicants' findings.

It should also be noted that, at the time the present invention was made, the common understanding in the art concerning optimal pH for expressing proteins through *Pichia* yeast expression systems was pH 5. Thus, one skilled in the art would not be motivated to select a pH different to that was understood to be "optimal." It was the present inventors who discovered that protein expression can be significantly enhanced by lowering the pH to 3 and that at this pH, MK protein degradation occurs much less than at pH 5 (see Example 3).

It is well established in the Patent Law finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, the cited references do not contain a suggestion of the claimed invention. It is only the applicants' disclosure that provides such a teaching, and the applicant's disclosure cannot be used to reconstruct the prior art for a rejection under §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d

> 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The mere fact that the purported prior art could have been modified or applied in a manner to yield applicants' invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection,"[b]oth the suggestion and the expectation of success must be founded in the prior art..." *In re Dow Chemical Co., supra* at 1531. In references cited in support of the §103 rejection, one finds neither. From the cited reference, at most, it may have been obvious to try to use the applicants' vectors and methods. However, the "obvious to try" standard has long been held to be an inappropriate basis for a §103 rejection. See, for example, *In re Antonie*, 195 USPQ 6 (CCPA 1977); *In re Dow Chemical Co.*, 5 USPQ2d 1529 (CAFC 1988). Certainly, the cited references do not disclose or suggest the surprising advantages of the subject invention. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §103.

In view of the foregoing amendments and remarks above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRS/la

Attachments: Petition and Fee for Extension of Time
Statement under 37 CFR §1.821
Sequence Listing on paper and computer readable format
Copy of specification as filed (excluding claims)
Copies of Figures 1-17 as filed